

REMARKS

Claims 1-59 were pending. Claims 1-56, 58 and 59 stand rejected. Claim 57 is withdrawn from consideration.

Claims 1, 9, 14-15, 21, 28, 42, 46-48, 51, 54, and 59 are amended. Claims 7-8, 10-13, 22-23, and 25 are canceled. Claims 2-6, 16-20, 24, 26-27, 29-41, 43-45, 49-50, 52-53, and 55-58 remain unchanged. Therefore, upon entry of this amendment, the pending claims are Claims 1-6, 9, 14-21, 24, and 26-59.

THE AMENDMENT

Claim 1 has been amended to include the step of crushing the aged gel into particulates of a particular size. Support therefor can be found, for example, in Claims 7 and 8, now canceled.

Claim 1 has also been amended to recite that the crushed gel particulates are suitable for incorporation into a microanalytical device. Support therefor can be found, for example at page 10, line 17 and page 11, lines 1-4 of the Specification. This amendment has necessitated cancellation of Claim 25, which is directed to monoliths, films and fibers.

Claim 9 has been amended to recite that the sol comprises a tetraalkyl orthosilicate and a silane, wherein the silane is substituted with a C₈-C₂₄ alkyl group and substituted with at least two leaving groups selected from OR and halo. Support therefor can be found, for example, in Claims 12 and 13, now canceled. The cancellation of Claims 12 and 13 has necessitated amending Claims 14 and 15 to correct their dependency. The amendment to Claim 9 has also necessitated cancellation of Claims 10-11, and the amendment to Claim 28.

Claim 9 has also been amended to recite that the matrix is incorporated into a microanalytical device and that the matrix is formed in situ. Support therefor can be found, for example at page 6, lines 6-7 and page 11, lines 1-4 of the Specification. This amendment has necessitated cancellation of Claims 22-23, which are directed to crushed gels.

Claim 46 has been amended to recite the formation of a bed. Support therefor can be found, for example, in Claim 44.

Claims 47 and 48 have been amended to correct their dependency.

Claim 59 has been amended to correct its dependency so that it no longer depend upon Claim 57, which is withdrawn.

Claims 15, 21, 42, 51 and 54 have been amended to delete reference to abbreviated terms, e.g., TEOS, RI, and so forth. Claim 42 has also been amended to correct the spelling of "lactase."

Neither the cancellation of claims nor the amendment of pending claims should be construed as abandonment of any canceled subject matter. Accordingly, the cancellation of claims or amendments herein is without prejudice to further prosecution in a continuation, continuation-in-part, divisional or other related application.

No new matter has been added.

THE PREVIOUS RESTRICTION REQUIREMENT

Restriction was previously required and Applicant elected to prosecute the claims of Group I, with the biological material being a polynucleotide, a gene or a gene fragment.

The Examiner has now reconsidered the restriction requirement and has rejoined the inventions of Groups I-III, with the biological material being a polynucleotide, a gene, a gene fragment, an enzyme, an antibody, a coagulation modulator, a cell membrane or a membrane fragment.

Claim 57 remains withdrawn from consideration as being directed to a non-elected invention.

OBJECTIONS TO THE CLAIMS

Claim 59 is objected to as containing the non-elected embodiment, specifically the non-elected embodiment recited in Claim 57.

Claim 59 has been amended so that it no longer depends from the withdrawn Claim 57. Applicant asserts that this amendment addresses the claim objection and withdrawal of the objection is respectfully requested.

REJECTION UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 46-55 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention. In particular, the term "bed" in Claims 47-48 has no antecedent basis as Claim 45, from which they depend, contains no recitation of a "bed."

Claim 46 has been amended to recite the formation of a bed. Claims 47 and 48 have been amended so that they now depend from Claims 44 and 46, both of which provide

antecedent basis for the term "bed." Applicant asserts that these amendments address the rejection and withdrawal of the rejection is respectfully requested.

Claims 49-55 do not recite the term "bed," and accordingly, Applicant believes that the requirements of 35 U.S.C. §112, second paragraph are met.

REJECTION UNDER 35 U.S.C. §102(e) OVER LIU

Claims 1-6, 9-11, 16-17, and 24-43 stand rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 6,303,290 to Liu et al. (hereinafter "Liu").

Liu is cited as teaching an alcohol-free method of making a porous, inorganic matrix with a biological material encapsulated therein. The Liu method comprises (a) forming an aqueous composition comprising a ceramic oxide colloidal sol mixed with an acidified oxide salt solution, which is transformed into a polymerizing hydroxide solution, and wherein the resulting composition has a pH ranging from 6.2 to 8.2; (b) adding to the composition an amount of the biological material in a physiologically acceptable-buffered solution to form a nanocomposite, where the ionic strength of the nanocomposite is adjusted to a physiologically acceptable level by the addition of salts; (c) gently shaking the nanocomposite until it becomes viscous; (d) shaping this viscous, aqueous mixture into a final form and aging into an aqueous gel; and (e) drying the aged gel slowly in air at about 4°C, thereby permitting a portion of the water in the gel to evaporate, where the drying gel has a decreased volume as compared with the aged gel, and molecules of the biological material are encapsulated within pores of the drying or dried gel.

Anticipation of a claimed invention by a prior art reference under 35 U.S.C. §102 requires the presence in a single prior art reference of each and every element of a claimed invention. Applicant respectfully submits that the cited reference to Liu fails to disclose each and every element of the presently claimed methods.

In particular, Liu fails to disclose the step of crushing the aged gel into particulates, which is recited in Claim 1, as amended. Claim 7, which forms the basis for this amendment, was not rejected under this reference and Applicant asserts that Claim 1, as presently amended, and the claims that depend therefrom, are patentable over the Liu teaching.

In addition, Liu fails to disclose a sol comprised of a tetraalkyl orthosilicate and a silane substituted with at least two leaving groups selected from the group consisting of OR and halo, which is recited in independent Claim 9, as amended. Claim 12, which forms the basis for this amendment, was not rejected under this reference and Applicant asserts that

Claim 9, as presently amended, and Claims 28-40, which depend therefrom, are patentable over the Liu teaching.

Accordingly, the rejection on this basis is traversed and withdrawal thereof is respectfully requested.

REJECTION UNDER 35 U.S.C. §102(b) OVER DUNN

Claims 1-6, 9-10, 12, 15-16, 18, 21, and 24-43 stand rejected under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 5,200,334 to Dunn et al. (hereinafter "Dunn").

Dunn is cited as teaching a process for the production of a porous, transparent sol-gel glass containing an alcohol sensitive active biological material entrapped therein comprising: (a) forming a single phase sol by mixing a metal alkoxide in a non-alcoholic medium comprising water and an acid catalyst in a container exposed to ultrasonic energy, where the mixture has a pH not greater than about 2; (b) removing the ultrasonic energy and raising the pH of the sol to about 5-7 by the addition of a buffering agent; (c) adding the active biological material to the buffered sol; (d) forming a gel and allowing the gel to age; and (e) allowing at least a portion of the water in the gel to evaporate so that the volume of the product is decreased and the active biological material is trapped in a monolith of the gel having a reduced volume.

As noted above, anticipation of a claimed invention by a prior art reference under 35 U.S.C. §102 requires the presence in a single prior art reference of each and every element of a claimed invention. Applicant respectfully submits that the cited reference to Dunn fails to disclose each and every element of the presently claimed methods.

In particular, Dunn fails to disclose the step of crushing the aged gel into particulates, which is recited in Claim 1, as amended. Claim 7, which forms the basis for this amendment, was not rejected under this reference and Applicant asserts that Claim 1, as presently amended, and the claims that depend therefrom, are patentable over the Dunn teaching.

In addition, Dunn fails to disclose a sol comprised of a tetraalkyl orthosilicate and a silane, wherein the silane is substituted with a C₈-C₂₄ alkyl group and substituted with at least two leaving groups selected from OR and halo, which is recited in Claim 9, as amended. Claim 13, which form the basis for this amendment, was not rejected under this reference and Applicant asserts that Claim 9, as presently amended, and Claims 15, 28-40, which depend therefrom, are patentable over the Dunn teaching.

Accordingly, the rejection on this basis is traversed and withdrawal thereof is respectfully requested.

REJECTION UNDER 35 U.S.C. §103(a) OVER DUNN OR LIU IN VIEW OF AVNIR

Claims 1, 7-8, 9, 12, and 22-23 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Dunn or Liu in view of US Patent No. 5,300,564 to Avnir et al. (hereinafter "Avnir").

To establish a *prima facie* case of obviousness, the Examiner must present prior art references which, when combined or modified, teach or suggest all the claim limitations. However, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings in order to teach or suggest all the claim limitations. In addition, there must be a reasonable likelihood of success, viewed in the light of the prior art. *Brown & Williamson Tobacco Corp. v. Phillip Morris Inc.* 229 F.3d 1120, 56 USPQ2d 1456, 1459 (CAFC 2000) citing *In re Dow Chem.*, 837 F2d 469, 473, 5 USPQ2d 1529, 1531 (CAFC 1988). Furthermore, the teaching or suggestion to make the claimed invention and the reasonable expectation of success must both be found in the prior art, and not in Applicant's disclosure. *In re Vaeck*, 947 F2d 488, 20 USPQ2d 1438 (CAFC 1991). Based upon the foregoing requirements, Applicant respectfully submits that the Examiner has failed to establish a *prima facie* case of obviousness.

Dunn is cited for the reasons noted above. The Office Action indicates that Dunn further teaches that it would be advantageous to encapsulate enzymes in a porous, transparent glass structures, such as those prepared by the sol-gel process. Such encapsulation is stated to be significantly easier to miniaturize, and would be far less cumbersome and far more reliable than membrane encapsulating systems. The Office Action indicates that Dunn does not explicitly teach that the aged gel is crushed into particulates, preferably between about 10-80 μ m in diameter.

Liu is cited for the reasons noted above. The Office Action indicates that Liu does not explicitly teach that the aged gel is crushed into particulates.

Anvir is thus cited as teaching a doped sol-gel that can be made in any shape, as teaching that doped sol-gel glasses can be used for all chromatographic purposes and that extraction or separation is performed by passing a solution through doped sol-gel columns, and for teaching that crushed powder sol-glasses may be used as support for enzymatic

column chromatography, with the exception that the glasses are ground to a 60-100 mesh size. As stated in the Office Action, it would have been obvious to the ordinary skilled artisan to modify the Dunn or Liu methods by further crushing the aged sol glasses into particulates in light of the Avnir teaching.

It is unclear why Claims 9 and 12 are rejected as being obvious over the combined Dunn and Avnir teachings or the combined Liu and Avnir teachings. Both Dunn and Liu fail to disclose a sol comprised of a tetraalkyl orthosilicate and a silane, wherein the silane is substituted with a C₈-C₂₄ alkyl group and substituted with at least two leaving groups selected from OR and halo, which is recited in Claim 9, as amended. This amended language is found in Claims 12-13. This failure by Dunn and/or Liu is not remedied by the Avnir teaching. The Office Action makes no assertion that Avnir teaches the use of the recited tetraalkyl orthosilicate and silane. Therefore, the following rebuttal will be directed to the Avnir teaching as it relates to crushed powder sol gel glasses, as applied to Claim 1.

The Office Action states that the ordinary skilled artisan would be motivated to carry out this modification since Avnir already teaches that crushed powder sol gel glasses may be used as a support for enzymatic column chromatography. However, there is no suggestion or motivation to combine this teaching with that of Dunn or Liu, to arrive at a method whereby the aged gel is crushed into particulates between about 10-80 μm in diameter and suitable for incorporation into a microanalytical device, as is recited in Claim 1. None of the references are directed to this utility and therefore there is no motivation to modify their teachings to arrive at a method of making a product that is tailored, by size and configuration, to be used in a microanalytical device. The Avnir teaching of a method of making 60-100 mesh size particles for use in enzymatic column chromatography, would not suggest to the ordinary skilled artisan that particles could be crushed to a different size for use in a different format. A range of 60-100 mesh size corresponds to 250-149 μm , a particle size range that is significantly larger than the 10-80 μm range presently recited in Claim 1.

The Office Action further states that an ordinary skilled artisan would have a reasonable expectation of success based on the teachings of Dunn and Avnir or Liu and Avnir. Again, a teaching of 60-100 mesh size particles that are useful in enzymatic column chromatography does not suggest that one could successfully modify this teaching to make particles of a much smaller size for use in a microanalytical device, as is recited in Claim 1.

Even if the Dunn or Liu teachings, were combined with the Avnir teachings, at best, one would have a teaching of 60-100 mesh size particles, which are not the same as or

suggestive of a crushed 10-80 μm particulate. Further, Applicant asserts that, in this case, size is not an arbitrary parameter. Avnir does not teach or suggest the use of these sol-gel materials in microanalytical devices. Therefore, the 60-100 mesh size teaching does not suggest the smaller sized particles that are suitable for incorporation into a microanalytical device, as recited in Claim 1.

In conclusion, Applicant asserts that a *prima facie* case of obviousness has not been established. Accordingly, since the cited Dunn or Liu, and Avnir references, whether viewed alone or in combination, do not suggest the invention as presently claimed, Applicant asserts that the invention is patentable under 35 U.S.C. §103(a) and respectfully request withdrawal of the rejection.

REJECTION UNDER 35 U.S.C. §103(a) OVER DUNN IN VIEW OF REETZ

Claims 1, 9, 12-14 and 18-20 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Dunn in view of Reetz et al. *Biotechnology and Bioengineering* 9:527-534 (1996) (hereinafter "Reetz").

As noted above, to establish a *prima facie* case of obviousness, the Examiner must present prior art references which, when combined or modified, teach or suggest all the claim limitations. There must be some suggestion or motivation to modify or combine the references in order to teach or suggest all the claim limitations. There must be a reasonable likelihood of success. Based upon the foregoing requirements, Applicant respectfully submits that the Examiner has failed to establish a *prima facie* case of obviousness.

Dunn is cited for the reasons noted above. The Office Action indicates that Dunn does not explicitly teach a method where the sol comprises a tetraalkyl orthosilicate and a silane substituted with at least two leaving groups selected from OR and halo, or where the silane is substituted with a C₈₋₂₄ alkyl group or where the alkyl group is C₁₈.

Reetz is thus cited as teaching that lipase activity in gels from a mixture of tetramethoxysilane and alkyltrimethoxysilanes was dramatically enhanced with increasing the amount and alkyl chain length of the hydrophobic silanes, including the alkyl group C₁₈.

As stated in the Office Action, it would have been obvious to the ordinary skilled artisan to modify the Dunn method by further introducing a substituted silane in light of the Reetz teaching, due to the stabilizing effect on entrapped lipase by increasing the amount and alkyl chain length of the silanes.

Dunn and Reetz fail to disclose the step of crushing the aged gel into particulates, which is recited in Claim 1, as amended. Claim 7, which forms the basis for this amendment, was not rejected under these combined references and Applicant asserts that Claim 1, as presently amended, and the claims that depend therefrom, are patentable over the combined Dunn and Reetz teachings.

Therefore, the following rebuttal will be directed to the Reetz teaching as it relates to Claims 9 and 12-14. Claim 9, as amended, is directed to a method for immobilizing a biological molecule in a porous inorganic matrix that is incorporated into a microanalytical device and which is formed *in situ*.

The Office Action states that the ordinary skilled artisan would be motivated to carry out this modification because increasing the amount and alkyl chain length of the silanes enhances lipase-doped sol, as taught by Reetz. Neither reference teaches or suggests forming a sol *in situ* in a microanalytical device. Therefore, even if the teachings were combined, they would not teach or suggest the invention as presently recited in Claim 9.

Therefore, in light of the amendments to the claims, Applicant asserts that the cited Dunn and Reetz references, whether viewed alone or in combination, do not suggest the invention as presently claimed, Applicant asserts that the invention is patentable under 35 U.S.C. §103(a) and respectfully request withdrawal of the rejection.

REJECTION UNDER 35 U.S.C. §103(a) OVER DUNN IN VIEW OF AVNIR, SWEDBERG AND
FREEMAN

Claims 44-56 and 58-59 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Dunn in view of Avnir, US Patent No. 6,240,790 to Swedberg et al. (hereinafter "Swedberg"), and US Patent No. 6,194,900 to Freeman et al. (hereinafter "Freeman").

As noted above, to establish a *prima facie* case of obviousness, the Examiner must present prior art references which, when combined or modified, teach or suggest all the claim limitations. There must be some suggestion or motivation to modify or combine the references in order to teach or suggest all the claim limitations. There must be a reasonable likelihood of success. Based upon the foregoing requirements, Applicant respectfully submits that the Examiner has failed to establish a *prima facie* case of obviousness.

Dunn is cited for the reasons noted above. More specifically, Dunn is cited for teaching that it is advantageous to encapsulate enzymes in a sol-gel and that such encapsulation is easier to miniaturize and is far less cumbersome than membrane

encapsulating systems. The Office Action indicates that Dunn does not explicitly teach a method of preparing a microanalytical device containing a sol-gel comprising an entrapped biological molecule, or a method of using the microanalytical device. Applicant asserts that there is nothing in Dunn that indicates that such advantages would be obtainable if the sol-gel was used in a microanalytical device. At best, one skilled in the art might try such a modification of the Dunn teaching, but there is nothing to suggest that such a modification would be successful.

Avnir is cited as teaching that doped sol-gel glass can be any shape and that it can be used for any purpose, in particular teaching that crushed powder sol gel glasses may be used as a support for enzymatic column chromatography. The combined teachings of Dunn and Avnir do not suggest the instantly claimed methods of preparing and using a microanalytical device (Claims 44-46) and improved microanalytical device (Claim 58). This failure is not remedied by the Swedberg and Freeman teachings.

Swedberg is cited as teaching a high-throughput microanalysis device having a plurality of sample processing compartments for use in analysis of solutes in the liquid phase. Freeman is cited a teaching a miniaturized total analysis system with an in-line NMR detection compartment for the analysis of solutes in the liquid phase.

As stated in the Office Action, it would have been obvious to the ordinary skilled artisan to modify the Dunn teachings by forming a microanalytical device containing biological material doped sol-gel and using the microanalytical device to analyze solutes in the liquid phase in light of the Avnir, Swedberg and Freeman teachings, because the encapsulated biological material prepared by the sol-gel process is easier to miniaturize and less cumbersome for use in high sensitivity analytical devices as taught by Swedberg and Freeman for achieving high throughput sample processing and analysis.

The mere fact that Dunn touts the benefits of its sol-gel and that Avnir describes the suitability of sol-gels enzymatic column chromatography is insufficient to suggest to one of skill the art that the teachings could *successfully* be modified for use in microanalytical devices. There must be some suggestion to make such modification and there must be a reasonable expectation of success, both of which are lacking. Both Swedberg and Freeman are directed to microanalytical devices having a unique configuration. Sample treatment, as well as analytical separation and detection, are described generically, as they appear to be of less significance to the invention than the device's configuration *per se*. Therefore, the

Swedberg and Freeman also do not provide the necessary motivation to modify the Dunn and Avnir sol-gel teachings so as to be adapted for use in a microanalytical device.

In conclusion, Applicant asserts that the cited Dunn, Avnir, Swedberg, and Freeman references, whether viewed alone or in combination, do not suggest the invention as presently claimed. Applicant asserts that the invention is patentable under 35 U.S.C. §103(a) and respectfully request withdrawal of the rejection.

SUMMARY

The above arguments and amendments to the Claims are submitted for the purpose of facilitating allowance of the Claims and a sincere effort has been made to place this application in condition for allowance. An early notice of allowance is earnestly requested.

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned at (650) 330-4916.

Respectfully submitted,

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